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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/921,144	08/01/2001	Caili Wang	13403.0004.NPUS00	6422

7590 07/21/2003

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EXAMINER

HELMS, LARRY RONALD

ART UNIT	PAPER NUMBER
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1642

DATE MAILED: 07/21/2003

15

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/921,144

Applicant(s)

WANG ET AL.

Examiner

Larry R. Helms

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 18 May 2003.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-93 is/are pending in the application.
- 4a) Of the above claim(s) 31-86 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-30 and 87-93 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
- 4) ☐ Interview Summary (PTO-413) Paper No(s) _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other:

DETAILED ACTION

1. Claims 1-93 are pending.
Claims 1-8, 17-24, 26-30, 87-90 and 93 have been amended.
2. Claims 31-86 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 9.
3. Claims 1-30, 87-93 are under examination.
4. The text of those sections of Title 35 U.S.C. code not included in this office action can be found in a prior Office Action.
5. The following Office Action contains some NEW GROUNDS of rejection.

Rejections Withdrawn

6. The rejections of claims 1-30, 87-93 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of the amendments to the claims.
7. The rejection of claims 20-21, 23-27 under 35 U.S.C. 102(b) as being anticipated by Pluckthun et al (Immunotechnology 3:83-105, 1997) is withdrawn in view of the amendments to the claims and arguments.

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The following are NEW GROUNDS of rejections

Claim Rejections - 35 USC § 112

8. Claims 20-30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 20-30 are indefinite for reciting the single chain antigen binding unit as shown in Figure 18 because the claim does not describe the molecule in figure 18. The molecule in figure 18 is not a single chain antibody or antigen binding unit. It is a single polypeptide with a S-S in the dimerization domain. The term single chain antigen binding unit by definition is a polypeptide in which the VH and the VL are directly connected by a linker. The molecules in Figure 18 do not show this.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 1-30, 87-93 are rejected under 35 U.S.C. 103(a) as being unpatentable over Glockshuber et al (Biochemistry 29:1362-1367, 1990) and further in view of Pack et al (Biochemistry 31:1579-1584, 1992) and Arndt et al (J. Mol. Biol. 295:627-639, 2000) and Queen et al (U.S. Patent 5,693,762, issued 12/97) and Kammerer et al (Biochemistry 38:13263-69, 1999).

The claims are summarized as a non single chain antigen binding unit that comprises a human VH linked to a coiled-coil and a human VL linked to a coiled coil and the coiled coils do not form homodimers and the coiled coils are GABA receptors, or neurotransmitters, hormones and there is a flexon flanked by the VL or VH and the binding unit is multivalent, multispecific, and has a label attached.

Glöckshuber et al teach strategies to stabilize an FV fragment due to its low stability. Glockshuber et al does not teach a heterodimerization domain or coiled-coils

or humanized antibodies or GABA receptors. These deficiencies are made up for in the teachings of Pack et al, Arndt et al, Queen et al and Krammerer et al.

Pack et al teach amphipathic helices to stabilize the interactions of Fv fragments and bispecific fragments and a cysteine residue at the end of the helix to form a disulfide bond (see Figure 1 and entire document).

Arndt et al teach coiled-coil peptides that do not form homodimers.

Queen et al teach humanized Fv and antibodies and labeled fragments.

Kammerer et al teach the GABA receptors and they do not form homodimers.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a non single chain Fv comprising a coiled-coil dimerization domain for dimerization of the VH and VL wherein the coiled coil is from a GABA receptor, neurotransmitters, hormones and the dimerization domains do not form homodimers and the dimerization domains are linked by a disulfide bond.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a non single chain Fv comprising a coiled-coil dimerization domain for dimerization of the VH and VL wherein the coiled coil is from a GABA receptor, neurotransmitters, hormones and the dimerization domains do not form homodimers and the dimerization domains are linked by a disulfide bond because Glockshuber et al teach strategies to stabilize the Fv fragment for use as therapeutics. In addition, it would have been obvious to stabilize the Fv fragment by using a coiled coil dimerization domain because Pack et al teach that the helices were

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stable and produced heterodimers and disulfide bonds at the ends of the domains and the Fvs bind antigen and Arndt et al teach coiled coils that only form heterodimers and Kammerer et al teach GABA receptors that only form heterodimers and it is obvious that one would only want heterodimers because the heterodimers would produce an antigen binding site of a VH and a VL. In addition, it would have been obvious to humanize the Fv and couple a label because Queen et al teach general methods for humanization to overcome problems of therapy with mouse antibodies. Because Pack et al teach a cysteine at the end of the dimerization domain, this would produce a single polypeptide chain as interpreted in claims 20 and 22. Thus, it would have been obvious to produce a Fv fragment that is stabilized by a heterodimerization domain in view of the teachings of Glockshuber that the Fv is not stable and in view of the teachings of Pack that helixes form stable dimers and Arndt who teaches coiled coils do not form heterodimers and it is obvious that to form a functional Fv a heterodimer of VH and VL are needed and one would obviously avoid homodimers.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Conclusion

11. No claim is allowed. The following prior art is noted for teaching a helix-stabilized Fv, Arndt et al (J. Mol. Biol. 221-228, 9/7/2001).

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12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (703) 306-5879. The examiner can normally be reached on Monday through Friday from 7:00 am to 4:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

13. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 308-4242.

Respectfully,

Larry R. Helms Ph.D.

703-306-5879

A handwritten signature in black ink, appearing to be 'L. Helms', written in a cursive style.